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BUBBLE-INDUCED LOCAL HYDROSTATIC PRESSURE GRADIENTS AS A POSSIBLE CAUSE OF DYSBARIC OSTEONECROSIS

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The most commonly held cause of dysbaric osteonecrosis is the temporary disruption of the local blood supply to the bone tissue by gas emboli or gas-induced thrombi or both (1,2). Such transient disruption of the blood supply during, and following, decompression is thought to result in the death of the bone cells (osteoblasts) due to local tissue anoxia. However, no one theory appears to explain adequately the pathogenesis of aseptic bone necrosis that has been observed in human bone tissue (3). A number of arguments have been put forward suggesting that disruption of the blood supply may not be the primary cause of aseptic bone necrosis. For example, Hills (4) has pointed out that bone cells are capable of living up to 12 h without an oxygen supply. Therefore, any ischemic mechanism causing bone necrosis would have to be operative for extended periods of time.

Recent work on the histopathology of inner-ear decompression sickness (DCS) in monkeys has indicated that rapid decompression from deep heliox dives (274 metres of sea water [msw]) can result in the local traumatic fracture of the hard temporal bone that encases the semicircular canals (5,6). Histological examination of the temporal bones of monkeys that were sacrificed within 2 weeks after the dive revealed full thickness breaks across the hard canal wall, as well as damage to the softer petrous tissue (Fig. 1). The presence of necrotic bone chips in the endolymphatic space further supports the indications that the temporal bone has suffered an extensive microfracture. Interference with the blood supply to the semicircular canals is also evident since blood vessels in the bone have been severely disrupted. Examination of the semicircular canals of squirrel monkeys sacrificed several months subsequent to a DCS-provoking dive revealed the presence of necrotic bone, the

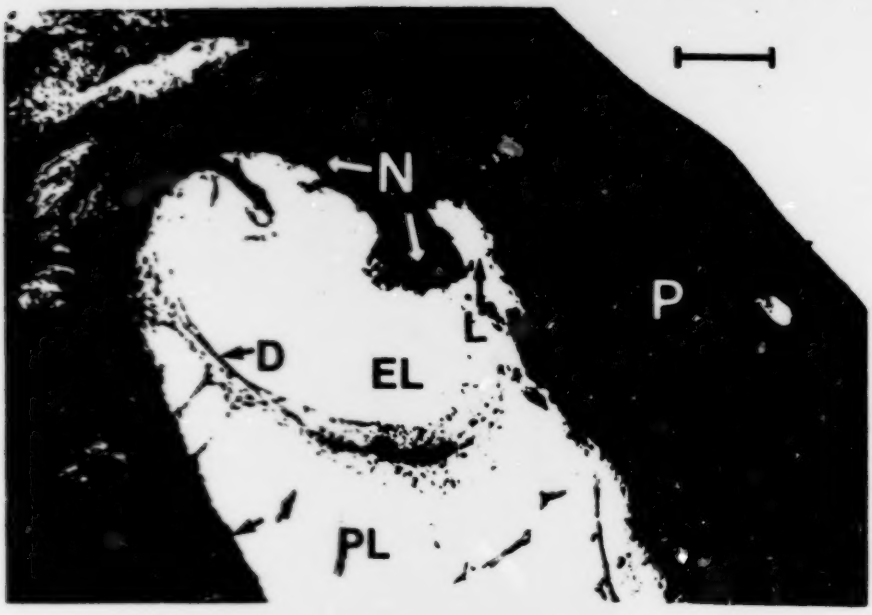

Fig. 1. Right lateral semicircular canal of *Monkey X* (8 days postdive survival) with extensive lesions of the canal wall (L) and the presence of necrotic bone (*N*) in the lumen of the canal. Abbreviations: *D* = lateral semicircular canal duct; *EL* = endolymphatic spaces; *PL* = perilymphatic space; *SC* = semicircular canal wall; *P* = petrous bone. Horizontal bar equals 0.1 mm.

growth of new bone and fibrous tissue, as well as extensive bone resorption. In many cases, new bone and tissue growth developed on the necrotic remains of the original bone (Fig. 2). The overall histological picture that is given by these specimens is almost identical to that which appears in accidental and experimentally induced temporal bone fractures (7,8).

Investigators have suggested that such localized trauma could explain the dysbaric osteonecrosis observed in human divers (9), because both gross fracture and local microfracture are known to lead to aseptic bone necrosis in nondiving populations (10). The hypothesis that a similar mechanism could be responsible for both syndromes is supported by the comparison of the histological results that are obtained after vestibular DCS incidents are detected in monkeys and aseptic bone necrosis is detected in humans and experimental animals. The presence of necrotic bone, resorption of bone by osteoclasts, new bone formation, hemorrhage, and prominent fibrosis have been observed in experimentally induced aseptic bone necrosis (11–13).

Several different mechanisms have been proposed to account for the DCS-induced extensive trauma that is found in the vestibular apparatus in the

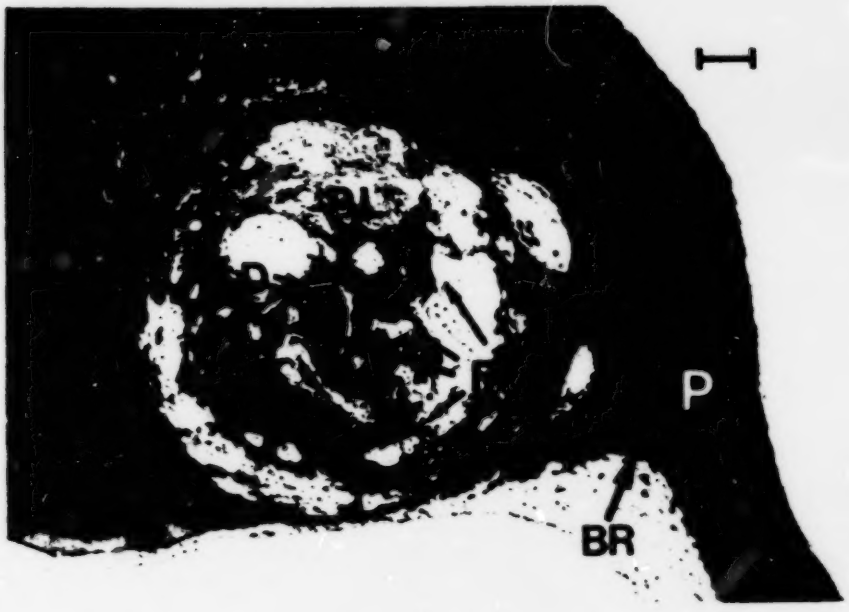

Fig. 2. Right posterior canal of *Monkey 117* (147 days postdive survival) with extensive destruction of the canal wall and surrounding petrous bone. There is resorption of petrous bone (*BR*) and the growth of fibrous and bony tissue in the endolymphatic and perilymphatic spaces (*FOL*). Abbreviations: *PL* = perilymphatic space; *EL* = endolymphatic spaces; *P* = petrous bone; *SC* = semicircular canal wall; *D* = semicircular canal duct. Horizontal bar equals 0.1 mm.

squirrel monkey (14). The most likely one appears to involve the growth of a bubble in a confined space where the boundaries surrounding the bubble would allow the development of a pressure gradient that is sufficient to produce temporal bone fracture. In this regard, it has been demonstrated that nucleation and bubble growth of hydrogen gas during the cooling of steel is capable of exerting pressures of 10 MPa or more, resulting in the formation of microcracks and the subsequent failure of the steel (14,15). The breakage of egg shells (16) and the rise in the hydrostatic pressure within the eyeball following bubble formation (17) both support the hypothesis that substantial trauma can occur this way in living tissue.

To determine if the local formation of a bubble in a rigid material, such as bone, could result in a pressure build-up sufficient to cause the fracture of bone, Ward et al. (18) developed a theoretical model of a bubble growing in a confined volume. To achieve this model, the investigators postulated that nucleation would occur in the reabsorption border of an osteoclast having a conical pit in its *brush-border* membrane in which nucleation and bubble

growth could occur. It was also assumed that the system was of constant mass (i.e., no gas diffusion in or out during bubble formation and growth) and constant volume (i.e., no flow of fluid or strain in the material to allow for relief of the pressure due to the bubble). The third assumption postulated that the hydrostatic pressure was applied to the system slowly, to allow the pressure to be transmitted to the enclosed volume as the material containing the volume relaxed under the stress.

The maximum pressure rise that could occur in the lacunae enclosing the bone cell was calculated using the conditions under which the squirrel monkeys were compressed and decompressed. The thermodynamic model was developed by determining the equilibrium values for the components of the system which maximized the Helmholtz function. The use of the Helmholtz function to describe the thermodynamic potential of the system is dictated by the constraints imposed on the model (i.e., constant mass, constant volume, and constant temperature). The model predicted that the maximum pressure rise in the lacunae of the bone would be slightly less than the pressure to which the animal had been compressed. By subjecting semicircular canal specimens of the squirrel monkeys to graded stress, investigators established that a pressure rise of this magnitude was more than sufficient to cause failure of the temporal bone (19).

It is to be emphasized that the pressure rise, as predicted by the model, would only occur if the fluid, or cell in which the bubble was growing, was contained in a fixed rigid volume (one in which the solution is unable to flow to release the stress generated by the bubble growing in the incompressible fluid). The stress developed by the growth of the bubble would also be dissipated by the elastic strain in the bone. However, traumatic failure of the bone will likely occur when the total strain is greater than 0.5% (20). Thus, unlike more elastic tissues in the body, bone is capable of only minor deformation before reaching a state of failure.

The basic premise of the model, that the bubble will generate a pressure rise, depends on the ability of the bone to contain the pressure as it develops. Bone cells are embedded in a calcium matrix that is believed capable of preventing both diffusional and volume flow transfer of water and metabolites (21). The only communication that the cells have with the blood supply is by way of bone canaliculi (less than 0.1 μm diameter) possessing narrow cellular membrane processes. Those cells farthest from the capillaries are supplied with metabolites by canaliculi that extend to cells lying closer to the blood. For rapid bubble growth, it is difficult to see how such processes could handle volume flow since the canaliculi are filled with membranous material. In other words, the bone is capable of functioning like a semipermeable membrane: it allows solute and water diffusion, but limits bulk volume flow.

A preliminary study has been performed to test the basic tenets of the model (i.e., that bubble formation will cause a local hydrostatic pressure rise). The results of a simple experiment are presented in Fig. 3. In this experiment, water was saturated with nitrogen at a pressure of 0.86 MPa in a thick-walled aluminum vessel and then decompressed to a pressure of 0.16 MPa. Following

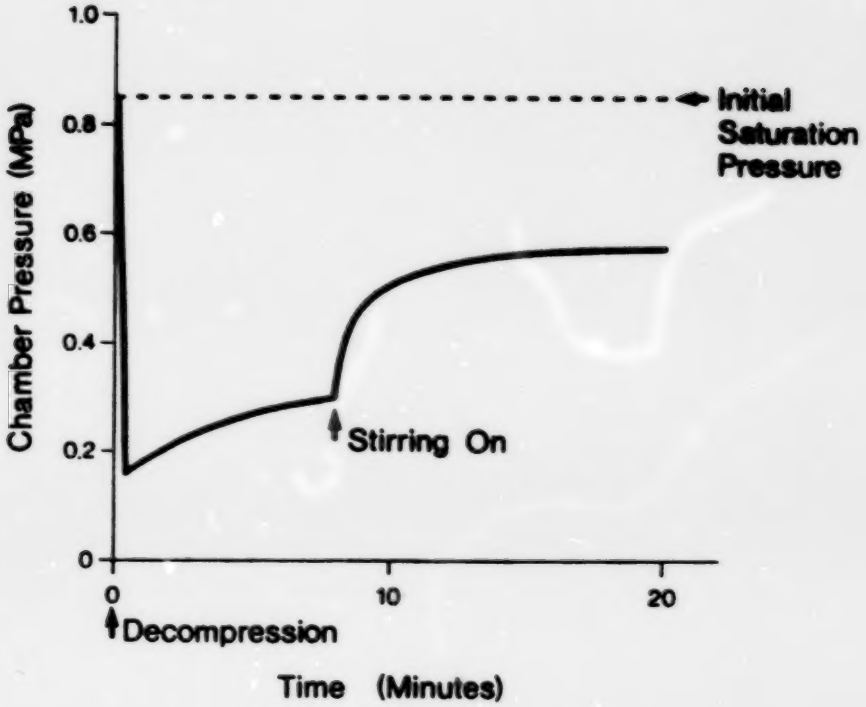

Fig. 3. The pressure rise in a thick-walled aluminum vessel filled with water that was rapidly decompressed to a pressure of 0.16 MPa after an initial saturation with nitrogen at 0.86 MPa. The increase in pressure corresponds to the growth of four small bubbles that were present in the vessel following decompression. The increase in pressure observed at 8 minutes is attributed to the renewed growth of the bubbles caused by an increased gas concentration near the bubbles that had been depleted by diffusion into the bubbles.

decompression, all valves to the system were closed and the pressure was monitored. Four small bubbles became visible and the pressure started to rise in the system along with their growth; stabilization occurred at a pressure of 0.57 MPa after about 20 min. The increase in pressure that was observed 8 min after the experiment started was attributed to the renewed growth of the bubbles caused by an increased gas concentration near the bubbles that had been depleted by diffusion into the bubbles. The rise in pressure to a value of 66% of the original saturation pressure strongly supports the validity of the theory. The pressure rise, measured experimentally, would not be expected to reach the predicted 90% of saturation pressure, because the container, the valve seals, and the plexiglass viewport will compress in response to the stress. Further experiments with a single bubble are underway to rigorously test the quantitative predictions of the theory.

In a similar experiment Kalser et al. (22) inserted a brass cannula that was filled with saline into the cortex of a freshly dissected dog femur. When the bone was decompressed in a hypobaric chamber, the pressure within the cannula rose to 8.0 kPa with respect to the chamber pressure. At the final altitude of 12 000 m the pressure in the bone fell as the interior of the bone approached equilibrium with the chamber pressure. After 15 min, the pressure within the bone increased again to reach a value of 16 kPa with respect to the chamber pressure; at that point, the experiment was terminated. Kalser et al. (22) concluded that the pressure rise was due to bubble formation within the interior of the femur. In this case, the pressure inside the bone reached 37% of the value at which it was originally saturated. This experiment indicates that the bone is capable of containing an elevated ambient pressure. The proposed theory accounts for the observed pressure increase.

In addition to the similarity in the histopathology of aseptic bone necrosis and vestibular DCS, there are other indicators which support the hypothesis that traumatic damage is occurring in the bone. Cockett et al. (23) and Mitano and Hayashi (24) have observed the presence of marrow-derived megakaryocytes in the lung after fatal DCS. This type of fat embolism usually occurs after fractures of large bones (25). Brickley-Parsons and Bradley (26) have shown that repetitive necrosis-inducing dives in mice resulted in the synthesis of an embryonic, hyperhydroxylated collagen of a type similar to the collagen that is formed during the healing of bone fractures.

Mechanical trauma, as a cause of aseptic bone necrosis, is not a new concept. Both Frost (27) and Lagier (28) have proposed that localized microfracture is the initial triggering mechanism for aseptic bone necrosis. The growth of bubbles within the bone provides a mechanism for this microfracture during decompression.

The epidemiological patterns associated with aseptic bone necrosis also support the concept of traumatic failure due to bubble growth within a confined volume. Because the local hydrostatic gradient associated with the bubble growth is a function of the saturation depth, deep saturation diving would tend to favor the development of severe trauma in the bones. This is in accord with the dramatic increase in the incidence of bone necrosis in diving as depth increases beyond 100 msw (29). Shallow saturation dives (e.g., in caisson work) would also tend to favor bone necrosis, since saturation of the poorly perfused bone would result. Though the theoretical pressure rise due to bubble growth is limited, bubble formation could still occur within the bone cells in the lacunae. Even if sufficient pressure to break the bone did not develop, cell death could still occur. If a sufficient number of cells were destroyed, then bone necrosis could result without either the traumatic failure or the disruption of the blood supply. This aspect of the model and our overall hypothesis is supported by the studies of Smith et al. (12) who observed the compression of an osteoblast cell against the walls of the bone lacunae by a bubble. Such a mechanism would also explain the development of aseptic bone necrosis after a single hyperbaric exposure (30). In this case, a signifi-

cant portion of the bone cells in critical sites may be damaged by localized bubble growth.

The low incidence of aseptic bone necrosis in the aviator can also be explained from this theory. The maximum pressure rise that can be generated by the growth of a bubble after hypobaric exposures is less than the original saturation pressure. Therefore, the maximum pressure rise will be less than 100 kPa (1 atm). The rate of change of pressure during decompression is also limited, therefore less stress develops.

One problem that the above model does not address pertains to the observation that aseptic bone necrosis appears to be linked to the compression phase of the dive, as well as the decompression portion of the dive profile (26,31). However, the rate of compression will affect the hydrostatic balance between the lacunae of the bone and the ambient pressure. If the rate of compression is sufficiently fast, then there will be large stresses that are set up at the boundaries between the fluid-filled cavities of the bone and the portion containing the calcium matrix. This stress occurs because of the difference in the elastic properties of the two media. The stresses and the resultant damage may explain the link between compression and aseptic bone necrosis, as well as account for the increase in serum ferritin levels that are observed during the compression phase of a dive, since such levels are believed to indicate damaged bone marrow cells (32).

Physical damage through growth of bubbles may be expected to occur in the more elastic tissues. If the properties of these tissues are such that the stress-strain curve has a small slope, then large deformations will be possible without permanent damage occurring. However, in a relatively inelastic tissue, such as the blood vascular wall, substantial bubble growth within the structure may cause extensive trauma, similar to that observed in bone. In this regard, Smith et al. (12) have detected several instances in which the epithelial lining of the arterioles was ripped away from the basement membrane of the vessel as a result of decompression.

By comparing the histology of vestibular DCS with that observed in experimental DCS, it may be concluded that a similar physical traumatic experience provides a likely explanation for the initial triggering of aseptic bone necrosis. The growth of a bubble in the enclosed lacunae of the bone has been shown to provide a probable mechanism to cause such damage. Experiments using isolated perfused tissues could be performed to test the theory. As well, a rigorous thermodynamic and mechanical analysis of the growth of bubbles in softer tissue is required. Such an analysis would have to include the mechanical properties of the tissues. This type of approach may provide useful information on the degree of damage that could occur in elastic and viscoelastic tissues such as the spinal cord and tendon during hyperbaric exposures.

Acknowledgments

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References

1. Gersh, I. Gas bubbles in bone and associated structures of guinea pigs decompressed from high pressure atmospheres. J Cell Comp Physiol 1945;26:101–117.
2. Jones PJ, Sakovich L. Fat embolism of bone. J Bone Joint Surg 1966;48–A:149–164.
3. McCallum, RI, Harrison, JAB. Dysbaric osteonecrosis: Aseptic necrosis of bone. In: Bennett PB, Elliott DH, eds. The physiology and medicine of diving. San Pedro: Best, 1982:488–506.
4. Hills BA. Decompression sickness. The biophysical basis of prevention and treatment. Chichester: John Wiley, 1977.
5. Fraser WD, Landolt JP, Money KE. Semicircular canal fracture in squirrel monkeys resulting from rapid decompression. Acta Otolaryngol 1983;95:95–100.
6. Landolt JP, Money KE, Topliff EDL, Nicholas AD, Laufer J, Johnson WH. Pathophysiology of inner ear dysfunction in the squirrel monkey in rapid decompression. J Appl Physiol: Respirat Environ Exercise Physiol 1980;49:1070–1082.
7. Altmann F. Healing of fistulas of the human labyrinth. Histopathological studies. Arch Otolaryngol 1946;43:409–415.
8. Perlman HB. Process of healing in injuries to the capsule of the labyrinth. Arch Otolaryngol 1939;48:48–49.
9. Fraser WD, Landolt JP, Money KE, Laufer J. Decompression-induced semicircular canal fractures in squirrel monkeys. In: Proceedings 7th Annual congress and symposium, European Undersea Biomedical Society, Cambridge, U.K. (July 21–24, 1981).
10. Manhin, HJ, Brower, TD. Bilateral idiopathic aseptic necrosis of the femur in adults: *Chandler's disease*. Bull Hosp Joint Diseases 1962;23:42–57.
11. Smith, KH, Stegall, P. Experimentally induced osteonecrosis in miniature swine. In: Beckman EL, Elliott DH, eds. Dysbarium-related osteonecrosis. Washington DC: U.S. Dept. of Public Health, 1974:105–112.
12. Smith KH, Stegall PJ, Harker LA, Slichter SJ, Richmond VL, Hall MH, Huang TW. Investigation of hematologic and pathologic response to decompression. Seattle, Wash: Virginia Mason Research Center, 1973. (Office of Naval Research Contract N00014–71–C–0273)
13. Catto M. Pathology of aseptic bone necrosis. In: Davidson JK, ed. Amsterdam: Excerpta Medica 1976:3–88.
14. Choo WY, Lee LY. Hydrogen trapping phenomenon in carbon steel. J Mater Sci 1982;17:1930–1935.
15. Hasnain, S. When the bubble bursts. Sci Dimension 1981;13(4):2.
16. Paganelli CV, Strauss RH, Yount DE. Bubble formation within hen's eggs. Aviat Space Environ Med 1977;48:48–50.
17. Cooke JP. Effects of helium and nitrogen upon intraocular pressure during near vacuum exposure. J Appl Physiol 1971;30:318–324.
18. Ward CA, Johnson WR, Venter RD, Ho BN, Forest TW, Fraser WD. Heterogeneous bubble nucleation and conditions for growth in a liquid-gas system of constant mass and volume. J Appl Physics 1983;1833–1843.
19. Venter RD, Ward CA, Ho S. Fracture studies on a mammalian semicircular canal. Undersea Biomed Res 1983;10:225–240.
20. Fung YC. Biomechanics. New York: Springer-Verlag, 1981.
21. Ham AW, Cormach DH. Histology. Philadelphia: J.P. Lippincott, 1979.
22. Kalser MH, Ivy HK, Pevsner JP, Marbarger JP, Ivy AC. Changes in bone marrow pressure during exposure to simulated altitude. Aviat Med (August) 1951:286–293.
23. Cockett ATK, Kado RT, Nakamura RM. The pathophysiology of decompression sickness. Revue de Physiologie Subaquatique 1969;1:199–202.
24. Mitano M, Hayashi K. Acute decompression sickness: An autopsy case with wide spread fat embolism. Acta Pathol (Japan) 1981;31:269–276.
25. Mohr JP, Fisher CM, Adams RD. Cerebrovascular disease. In: Petersdorf RG, ed. Principles of internal medicine. New York: McGraw Hill, 1976:1832–1868.
26. Brickley-Parsons D, Bradley ME. Abnormal bone and cartilage collagen metabolism in experimentally induced dysbaric osteonecrosis. In: Bachrach AJ, Matzen MM, eds. Underwater physiology VII:

Proceedings of the seventh symposium on underwater physiology. Bethesda: Undersea Biomedical Society, Inc., 1981:837–846.
27. Frost HM. The etiodynamics of aseptic necrosis of the femoral head. In: Proceedings conference of aseptic necrosis of the femoral head. St. Louis: National Institutes of Health, 1964:393–414.
28. Lagier R. Idiopathic aseptic necrosis of the femoral head. In: Zinn WM, ed. Idiopathic ischemic necrosis of the femoral head in adults. Stuttgart: Georg Thieme, 1983:49–65.
29. Underwater Engineering Group. Aseptic bone necrosis in commercial divers. UEG Technical Note 25, 1981.
30. James CCM. Late bone lesions in caisson disease. Lancet 1945;2:6–8.
31. Hills BA, Straley R. Aseptic osteonecrosis: A study of tibial blood flow under various environmental conditions. Aerosp Med 1972;43:724–728.
32. Gilman SC, Biersner RJ, Piantadosi C. Serum ferritin increases during deep saturation dives. Aviat Space Environ Med 1982;53:1014–1016.

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